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EXAMINER
LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/779,376	FAN ET AL.	
	Examin r	Art Unit	
	Frank W Lu	1655	

-- The MAILING DATE of this communication appears on th cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,9-16,19-23,26 and 30-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,9,10,12-16,19-23,26 and 30-38* is/are rejected.

7)☒ Claim(s) *11 and 12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *14 November 2002* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 3, 2003 has been entered. The claims pending in this application are claims 5, 9-16, 19-23, and 30-38. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the amendment filed on June 3, 2003.

Drawings

2. The proposed drawing correction and/or the proposed substitute sheets of drawings, filed on November 14, 2002 have been approved. A proper drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The correction to the drawings will not be held in abeyance. Note that applicant does not address this issue.

Claim Objections

3. Claim 9 is objected to because of the following informalities: "eluting said probe off said solid support" should be "eluting said probe from said solid support".

Appropriate correction is required.

The examiner notes that applicant does not address this issue.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

5. Claims 5, 13, and 32 are rejected under 35 U.S.C. 102(e) as being anticipated by Barany *et al.,* (US Patent No. 6,027,889, filed on May 28, 1997).

Barany *et al.,* teach detection of nucleic acid sequence differences using coupled ligase detection and polymerase chain reactions. As shown in Figures 12-17, a first oligonucleotide probe having a target-specific portion and a 5' upstream primer-specific portion, and a second oligonucleotide probe having a target-specific portion and a 3' downstream primer-specific portion were hybridized adjacent to one another on a corresponding target nucleotide sequence and were ligated together in a ligase chain reaction. However, if there was a mismatch in ligation end of the first or second probe, this mismatch would interfere with such ligation. Then unligated the first probe and the second probe were removed with Exo I and PCR-amplified using an upstream primer containing the same sequence as the 5' upstream primer-specific portion of the ligation product sequence (in the first probe) and a downstream primer complementary to the 3' downstream primer-specific portion of the ligation product sequence (in the second probe)

wherein one primer had a detectable reporter label. Finally, PCR products were hybridized with a DNA array with different capture oligonucleotides immobilized at different particular sites and had nucleotide sequences complementary to the unique nucleotide sequences across the ligation junctions of given probe sets, and the labels of the PCR products captured on the DNA array at particular sites were detected as recited in steps f) and g) of claims 5 and 32 (see Figures 12-17 and columns 9, 10, 25-28, and 79-90). Note that: (1) the first probe and second probe are considered as first and second ligation probe as recited in claims 5 and 32; (2) 5' upstream primer-specific portion in the first probe is considered to have two parts: UUP and an adaptor sequence as recited in claims 5 and 32 while 3' downstream primer-specific portion in the second probe is considered as DUP as recited in claims 5 and 32; (3) since claims 5 and 32 do not require that step c) must perform before step d), Exo I digestion step is considered as step c) recited in claims 5 and 32; (4) as shown in Figure 12, base G in left probe (a first ligation probe) that hybridizes to mutant sequence is considered as a first base at an interrogation position as recited in claim 5 or an interrogation position that is complementary to said detection position in a first ligation probe as recited in claim 32; and (5) claim 13 is considered as basic PCR steps including repeated denaturation, annealing and extension.

Therefore, Barany *et al.,* teach all limitations recited in claims 5, 13, and 32.

Response to Arguments

In page 10, second paragraph bridging to page 11, second paragraph of applicant's remarks, applicant argues that "[B]arany et al. does not teach or suggest methods that include hybridization of probes to a target, priming site (UUP); b) a second portion comprising a first

target-specific sequence and an interrogation position that is complementary to said detection position; c) a third portion comprising a downstream universal priming site (DUP); d) a fourth portion comprising a second target-specific sequence; and e) a fifth portion comprising an adapter sequence contained on at least one of said first and second ligation probes.".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection because Barany *et al.,* do teach an adapter sequence in the ligation primer since 5' upstream primer-specific portion in the first probe (ie., first ligation probe taught by Barany *et al.,*) are considered to have two parts: UUP and an adaptor sequence as recited in claims 5 and 32.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 14-16 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany *et al.,* (1997) as applied to claims 5, 13, and 32 above, and further in view of Walt *et al.,* (US Patent No. 6,327,410 B1, filed on September 11, 1998).

The teachings of Barany *et al.,* have been summarized previously, *supra.*

Barany *et al.,* do not disclose an array recited in claims 14-16 and 34.

Walt *et al.*, do teach an array comprising a substrate such as a fiber optical bundle recited in claims 16 and 34 with a patterned surface with discrete sites such as wells recited in claim 15 and a population of microspheres comprising at least a first subpopulation and a second subpopulation wherein said first subpopulation comprises a first nucleic acid and second subpopulation comprises a second nucleic acid, and wherein said microspheres are randomly distributed on said surface such that said discrete sites contain microspheres recited in claim 14 (see Figures 7A and 7B, columns 3, 4, and 28-30).

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claims 5 and 32 using an array recited in claims 14-16 and 34 in view of the patents of Barany *et al.,* and Walt *et al.*. One having ordinary skill in the art would have been motivated to modify the method of Barany *et al.,* because the simple replacement of one kind of nucleic acid array (a regular oligonucleotide array) from another kind of nucleic acid array (an array with microspheres having immobilized nucleic acids) during the process of determining the

identification of a nucleotide at a detection position in a target sequence would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement of one kind of nucleic acid array from another kind of nucleic acid array during the process of determining the identification of a nucleotide at a detection position in a target sequence would not change the method steps of the experiment.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 11, third paragraph bridging to page 13, first paragraph of applicant's remarks, applicant argues that: (1) neither of patents from Barany *et al.,* and Walt *et al.,* contains the element of a ligation probe comprising an adapter sequence; and (2) "one of ordinary skill in the art would not have been motivated to modify or combine Walt and Barany to reach the claims of the present invention because, 1) as stated above there is no teaching or suggestion in either reference of modifying either reference or combining them to reach the claims of the present invention of method of determining the identification of a nucleotide at a detection position in a

target through the use of ligation probes wherein the ligation probes collectively comprise the five portions as cited herein (which none of the cited references teach or suggest) and capturing the ligated probes on an array of capture probes where the array further comprises first and second subpopulations of microspheres and a substrate comprising discrete sites (claim 14), where discrete sites are wells (claim 15) and where the substrate comprises a fiber optic bundle (claim 16) or where the substrate comprises discrete which are wells and the substrate further comprises a fiber optic bundle (claim 34).".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, Barany *et al.,* do teach an adapter sequence in the ligation primer since 5' upstream primer-specific portion in the first probe (ie., first ligation probe taught by Barany *et al.,*) are considered to have two parts: UUP and an adaptor sequence as recited in claims 5 and 32. Second, in response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, since Barany *et al.,* teach all limitations of the claims except the array recited in claims 14-16 and 34 that discloses by Walt *et al.*, the simple replacement of one kind of nucleic acid array (a regular oligonucleotide array) from another kind of nucleic acid array (an array with microspheres having immobilized nucleic acids) during the

process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement of one kind of nucleic acid array from another kind of nucleic acid array during the process of determining the identification of a nucleotide at a detection position in a target sequence would not change the method steps of the experiment.

8. Claims 10-13, 19-22, 26, 31, 33, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang *et al.,* (US Patent No. 5,876,924, filed on July 31, 1996) in view of Barany *et al.,* (1997).

Regarding claims 10, 13, 19-22, 26, 31, 33, and 35, Zhang *et al.,* teach nucleic acid amplification method hybridization signal amplification method. As shown in Figures 1 and 2, the two oligonucleotide probes (Capture/Amp-probe-1 and Amp-probe-2) were first hybridized adjacent to one another on a corresponding target nucleotide sequence of the target nucleic acid in a sample wherein the Capture/Amp-probe-1 was 3'-biotinylated. Then the complex comprising target nucleic acid-probes was separated from any unbound reactants using streptavidin-coated paramagnetic beads as recited in claims 10, 19, 20, and 31 and the probes were ligated together in a ligation chain reaction. Ligated product of Capture/Amp-probe-1 and Amp-probe-2 were used as a template for PCR (see Figures 1 and 2, and columns 10-17). This method could be used to detect a single mutation in a target (see column 6, first paragraph). Note that: (1) since claims 26 and 33 do not require that step a) must perform before step b), binding of target nucleic acid-

probe complex to streptavidin-coated paramagnetic beads is considered to provide a support on which the target sequence is immobilized recited in step a) of claims 26 and 33; (2) (d) domain of Capture/Amp-probe-1 is considered as DUP while (g) domain of AMP-PROBE-2 is considered to have two parts: UUP and adaptor sequences; (3) streptavidin-coated paramagnetic beads are considered as a double-stranded moiety as recited in claim 10 since they bind to and separate the complex comprising target nucleic acid-probes which is double stranded from any unbound reactants; (4) the target nucleic acid is considered to be indirectly immobilized on streptavidin-coated paramagnetic beads as recited in claims 19 and 21; (5) biotinylated Capture/Amp-probe-1 is considered as a functional attachment moiety recited in claim 22 since this probe attaches the target nucleic acid to streptavidin-coated paramagnetic beads in the target nucleic acid-probe complex; and (6) a base located in 5' of capture/AMP-probe is considered as an interrogation position as recited in claims 26 and 33 (see Figure 1).

Zhang *et al.,* do not disclose steps g) and h) of claims 26 and 33.

The teachings of Barany *et al.,* have been summarized previously, *supra.* Barany *et al.,* also teach steps g) and h) of claims 26 and 33 (see above).

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claims 26 and 33 using a PCR product made by Zhang *et al.,* as a hybridization probe in view of the patents of Barany *et al.,* and Zhang *et al.*. One having ordinary skill in the art would have been motivated to modify the method of Barany *et al.,* because the simple replacement of one well known LDR/PCR method (LDR/PCR method of Barany *et al.,*)

from another well known LDR/PCR method (LDR/PCR method of Zhang *et al.,*) in order to make a hybridization probe would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since using different methods to make a hybridization probe would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 13, second paragraph bridging to page 15, first paragraph of applicant's remarks, applicant argued that: (1) "[S]ince neither Zhang nor Barany teach or suggest hybridization of probes to a target, wherein the probes include the five portions outlined herein, the requirement that the prior art reference (or references when combined) must teach or suggest all the claim limitations has not been met. ."; and (2) "there is lacking any motivation to modify or combine reference teachings. First of all contrary to the Examiner's characterization of Zhang as an LDR process like Barany, they operate in distinctly different ways. The LDR process of Barany uses hybridization probes directed to extension products (amplified products). In contrast, Zhang is directed to methods where the target is first captured through the use of capture probes and

paramagnetic beads, then ligation occurs while still attached to the beads and after there is a release of the ligated amplification sequence from the beads, then there is amplification using a suitable PCR technique. See Zhang et al. at column 15, lines 35-41. lf the proposed modification or combination of the prior art would change the principle operation of the prior art being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 195%. Here the combination of the references would require substantial reconstruction and redesign of the elements shown in the primary reference (Zhang et al.) as well as a change in the basic principle under which Zhang et al. was designed to operate.

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, Zhang *et al.,* do teach the ligation probe comprising an adapter sequence since (g) domain of AMP-PROBE-2 is considered to have two parts: UUP and adaptor sequences. Second, in response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, although the examiner agrees with applicant that the process taught by Barany *et al.,* and the process taught by Zhang *et al.,* have different method steps, both processes include a common method step, ligation chain reaction. Since Zhang *et al.,* teach all limitations in

claims 26 and 33 except steps g) and h) while Barany *et al.,* disclose steps g) and h) of claims 26 and 33. Since the knowledge of LDR/PCR method was generally available to one of ordinary skill in the art at time the invention was made, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claims 26 and 33 using a PCR product made by Zhang *et al.,* as a hybridization probe in view of the patents of Barany *et al.,* and Zhang *et al.,* because the simple replacement of one well known LDR/PCR method (LDR/PCR of Barany *et al.,*) from another well known LDR/PCR method (LDR/PCR of Zhang *et al.,*) in order to make a hybridization probe would not change the experimental results.

9. Claims 9, 23, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang *et al.,* (1996) in view of Barany *et al.,* (1997) as applied to claims 13, 19-22, 26, 31, 33, and 37 above, and further in view of Seradyn Particle Technology (November 1996).

The teachings of Zhang *et al.,* and Barany *et al.,* have been summarized previously, *supra.*

Seradyn Particle Technology (page 7) confirms that streptavidin-coated paramagnetic beads taught by Zhang *et al.,* comprise a plastic material as recited in claims 23 and 30 since these beads has polystyrene core.

Zhang *et al.,* Barany *et al.,* and Seradyn Particle Technology do not disclose claim 9 wherein the target sequence is labeled with a binding ligand. However, Zhang *et al.,* teach steps

b) to d) in claim 9 except the probe is labeled with a binding ligand in step a) (see column 8 and 10-13).

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have removed non-hybridized probes using a method recited in claim 9 in view of the prior art of Barany *et al.*, Zhang *et al.*, and Seradyn Particle Technology. One having ordinary skill in the art would have been motivated to modify the method of Zhang *et al.*, because a method for labeling different nucleic acids with a binding ligand was known in the art at the time the invention was made and the simple replacement of one well known nucleic acid separation method (based on the interaction between a ligand on a target nucleic acid with its binding partner) from another well known nucleic acid separation method (based on the interaction between a ligand on a nucleic acid probe with its binding partner) during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since using different methods to remove non-hybridized probes would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 15, second paragraph bridging to page, last paragraph of applicant's remarks, applicant argues that: (1) "none of the references alone or in combination teach or suggest hybridization of probes to a target, wherein the probes collectively include the five portions outlined herein."; and (2) "there is lacking any motivation of modifying or combining the reference teachings. The Examiner's statement that it would have been obvious to replace one known method of nucleic acid separation with another known method does not provide the specific guidance required to provide motivation to modify or combine the references of Zhang, Barany and Seradyn to reach the claims of the present invention. 'obvious to try' is not the standard and the very general statement that the Examiner points to that one known method can be simply replaced with another known method with modification of Barany does not provide specific guidance on how to reach the claims of the present invention".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, Zhang *et al.,* do teach the ligation probe comprising an adapter sequence since (g) domain of AMP-PROBE-2 is considered to have two parts: UUP and adaptor sequences. Second, in response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some

teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, since Seradyn Particle Technology (page 7) only uses to confirm that streptavidin-coated paramagnetic beads taught by Zhang *et al.,* comprise a plastic material as recited in claims 23 and 30, as shown in above, the combination of Zhang *et al.,* Barany *et al.,* and Seradyn Particle Technology teach all limitations recited in claims 9, 23, and 30. Therefore, the simple replacement of one well known nucleic acid separation method (based on the interaction between a ligand on a target nucleic acid with its binding partner) from another well known nucleic acid separation method (based on the interaction between a ligand on a nucleic acid probe with its binding partner) during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since using different methods to remove non-hybridized probes would not change the experimental results. Third, since according to M.P.E.P. at 2144.07 and 2144.09, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose , the rejection made by the examiner is not "obvious to try" as suggested by applicant.

10. Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang *et al.,* (1996) in view of Barany *et al.,* (1997) as applied to claims 13, 19-22, 26, 31, 33, and 35 above, and further in view of Monforte *et al.,* (US Patent No. 5,830,655, published on November 3, 1998).

The teachings of Zhang *et al.,* and Barany *et al.,* have been summarized previously, *supra.*

Zhang *et al.,* and Barany *et al.*, do not disclose that said target sequence is attached to said support by direct chemical attachment of said target sequence to said support as recited in claim 37.

Monforte *et al.,* teach to immobilize nucleic acid templates by attachment to a solid support before a primer extension assay. Immobilization was via a covalent or non-covalent linkage (see last paragraph of column 6 and claims 1-3 in column 63).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 26 or 33 by attaching target sequences taught by Zhang *et al.,* onto a solid support in view of the patent of Monforte *et al.*. One having ordinary skill in the art would have been motivated to do so because Monforte *et al..,* have successfully attached nucleic acid templates to a solid support before amplification of the nucleic acid templates and the immobilization of the nucleic acid templates to a solid support would enhance to separate hybridized complexes formed by the nucleic acid templates and hybridized probes from unhybridized probes and the simple replacement of one well known nucleic acid separation method (based on the interaction between a ligand on a target

nucleic acid with its binding partner that immobilizes on a solid support taught by Zhang *et al.,*) from another well known nucleic acid separation method (based on the interaction between ligation probes with target sequences immobilized on a solid support) during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since using different methods to remove non-hybridized probes would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

11. Claim 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang *et al.,* (1996) in view of Barany *et al.,* (1997) and further in view of Monforte *et al.,* (1998) as applied to claims 13, 19-22, 26, 31, 33, 35, and 37 above, and further in view of Brown *et al.,* (US Patent No. 5,807,522, published on September 15, 1998).

The teachings of Zhang *et al.,* Barany *et al.,* and Monforte *et al.,* have been summarized previously, *supra.*

Zhang *et al.,* Barany *et al.*, and Monforte *et al.,* do not teach that said target sequence is attached to said support by absorption of said target sequence on said support wherein said support comprises charged groups as recited in claim 36.

Brown *et al.,* teach to immobilize nucleic acids onto a support comprising charged groups (ie., a slide with a layer of poly-l-lysine) (see column 16).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 26 or 33 by attaching target sequences taught by Zhang *et al.,* onto a solid support comprising charged groups in view of the patents of Monforte *et al.,* and Brown *et al.*. One having ordinary skill in the art would have been motivated to do so because, due to interaction between negative charges of the nucleic acids and positive charges of the support, immobilization of nucleic acids onto a solid support comprising positive charged groups would increase efficiency of the immobilization and the simple replacement of one solid support (ie., the support taught by Monforte *et al.*.) from another solid support (ie., the support with positive charges taught by Brown *et al.*) during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since using different methods to remove non-hybridized probes would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their

expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

12. Claim 38 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang *et al.,* (1996) in view of Barany *et al.,* (1997) and further in view of Monforte *et al.,* (1998) as applied to claims 13, 19-22, 26, 31, 33, 35, and 37 above, and further in view of Johnson *et al.,* (US Patent No. 6,372, 813, published on June 25, 1999).

The teachings of Zhang *et al.,* Barany *et al.,* and Monforte *et al.,* have been summarized previously, *supra.*

Zhang *et al.,* Barany *et al.*, and Monforte *et al.,* do not teach that said target sequence is attached to said support by photocrosslinking said target sequence to said support as recited in claim 36.

Johnson *et al.,* teach to photocrosslink a nucleic acid onto a solid support (see example 5, column 21).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 26 or 33 by attaching target sequences taught by Zhang *et al.,* onto a solid support by photocrosslinking in view of the patents of Monforte *et al.,* and Johnson *et al.*. One having ordinary skill in the art

would have been motivated to do so because Johnson *et al..,* have successfully photocrosslinked a nucleic acid onto a solid support and the simple replacement of one well known nucleic acid immobilization method (an immobilization method taught by Monforte *et al.,*) from another well known nucleic acid immobilization method (an immobilization method taught by Johnson *et al.,*) during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since using different methods to remove non-hybridized probes would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Conclusion

13. Claim 11 and 12 are objected to as being dependent upon a rejected base claim, but appears to be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

14. No claim is allowed.

15. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the patent Analyst of the Art Unit, Ms.Chantae Dessau, whose telephone number is (703) 605-1237.

Frank Lu
September 17, 2003

ETHAN WHISENANT
PRIMARY EXAMINER